Diabetes and intelligence? No, genes, intelligence and, then, diabetes

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No, genes, intelligence and, then, diabetes

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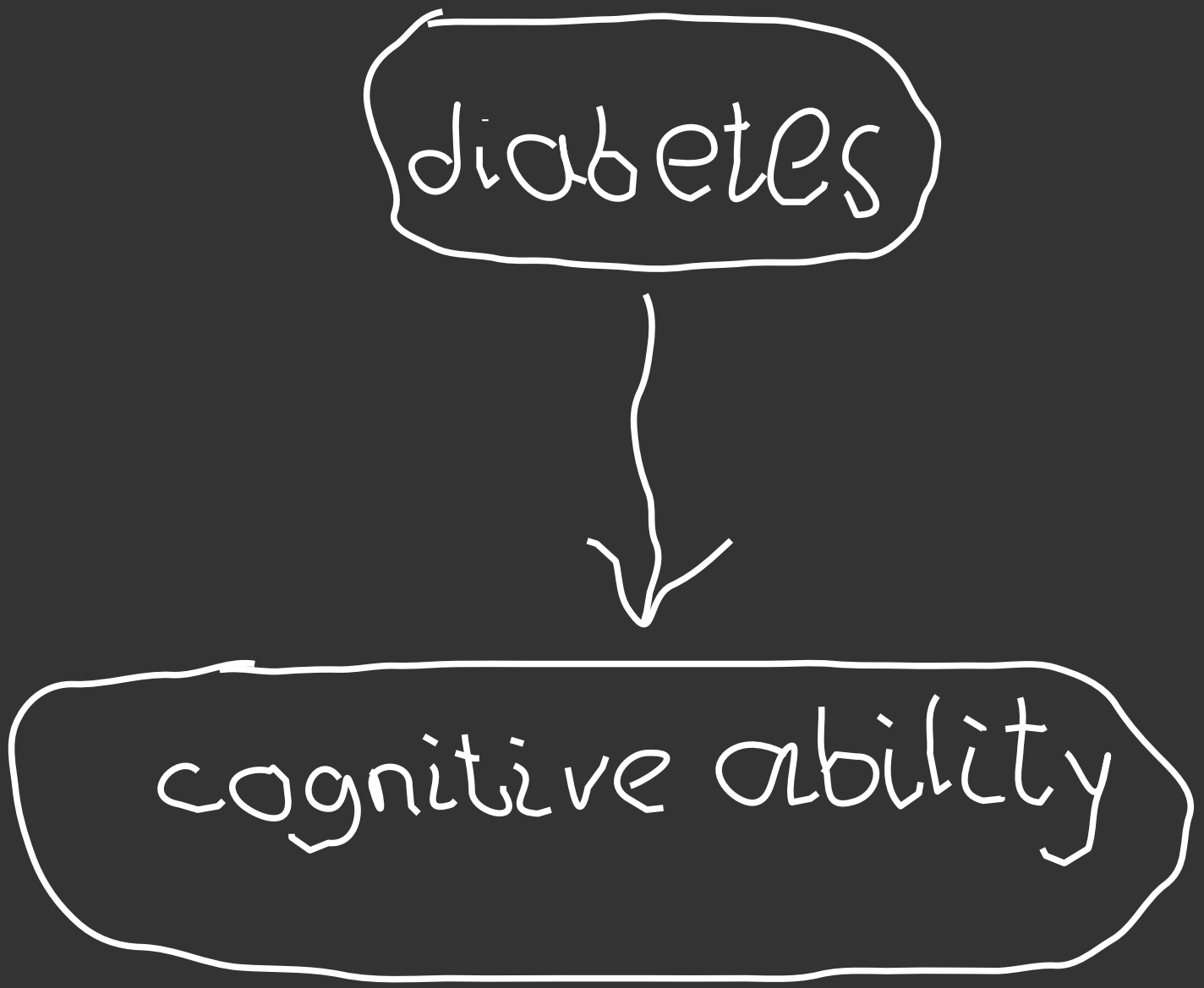
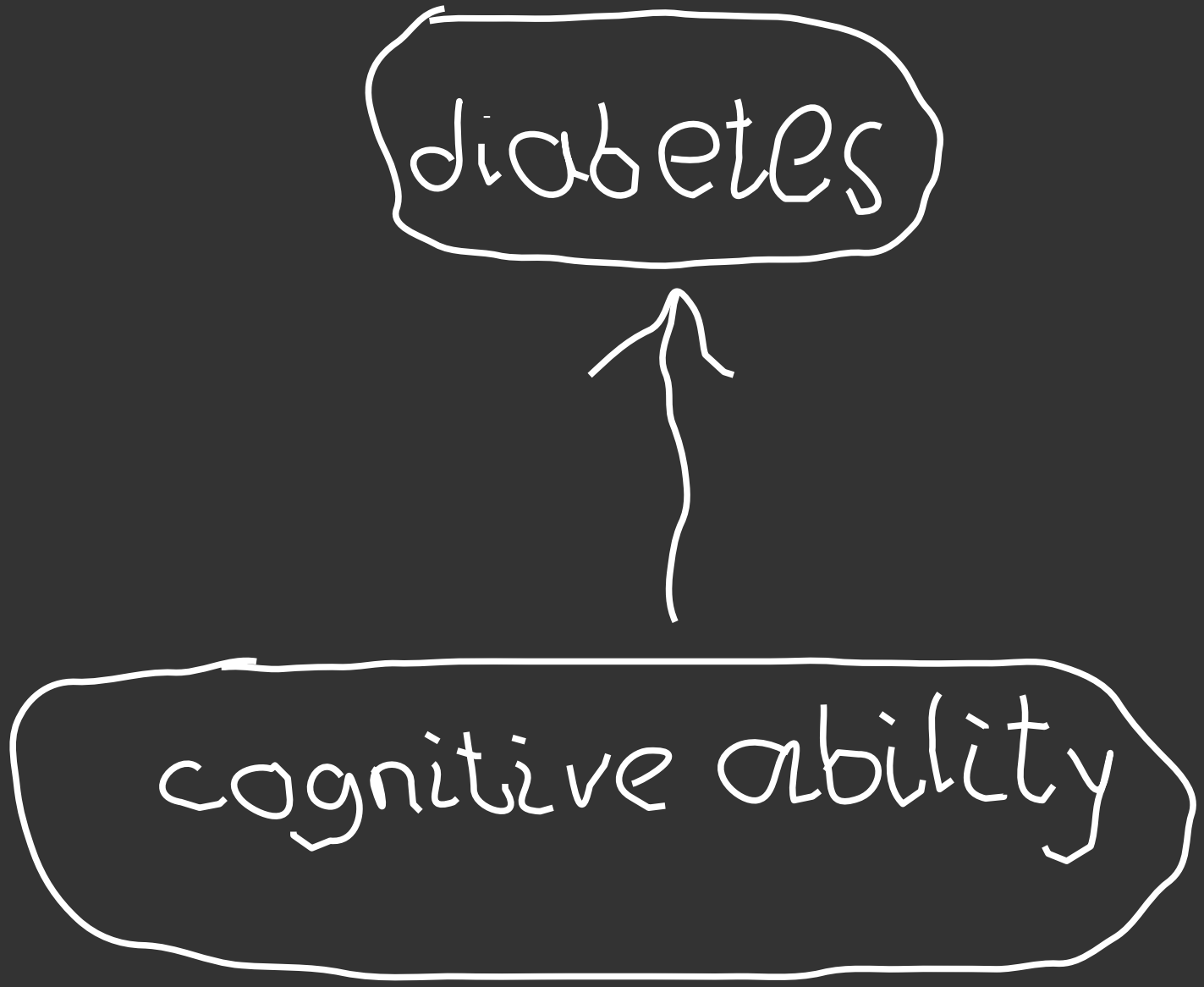
A common belief:
Diabetes impairs cognition

- Various possible pathways:
  - glycemic instability
  - inflammation etc


diabetes
cognitive ability

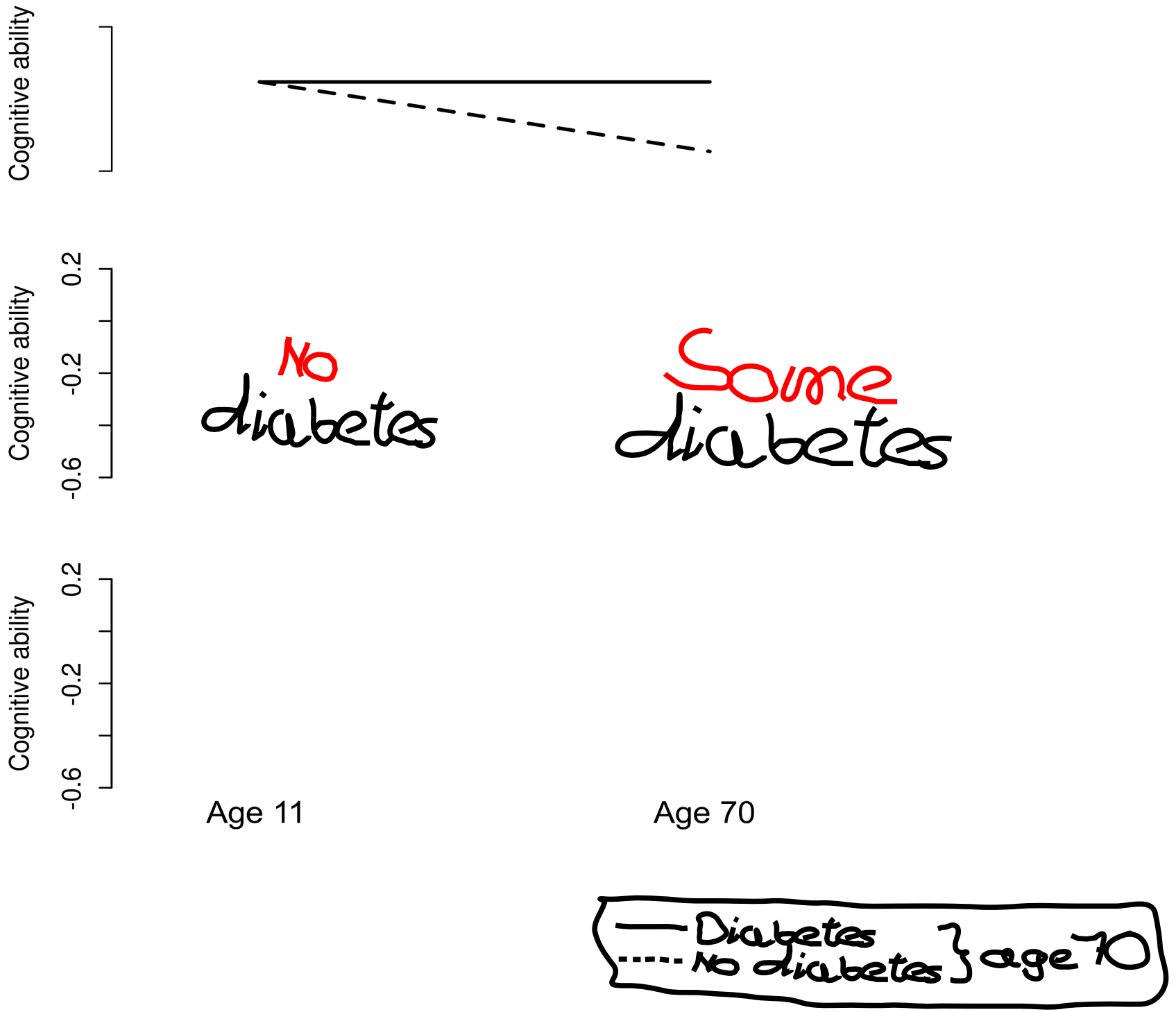
And yet we know:

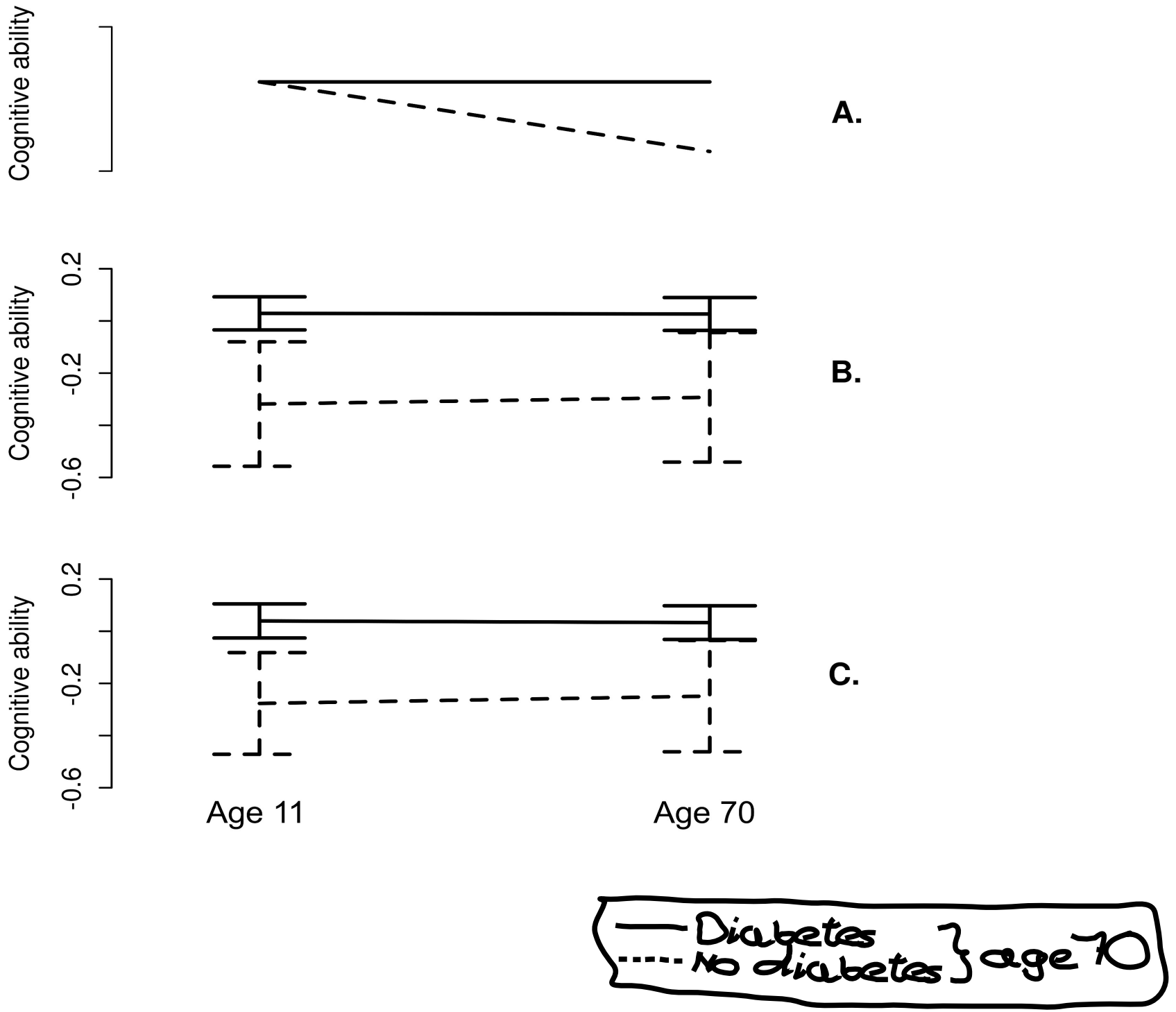
- People who set out with lower abilities tend to:
  - eat worse
  - exercise less
  - have higher body weights
  - are therefore at higher diabetes risk

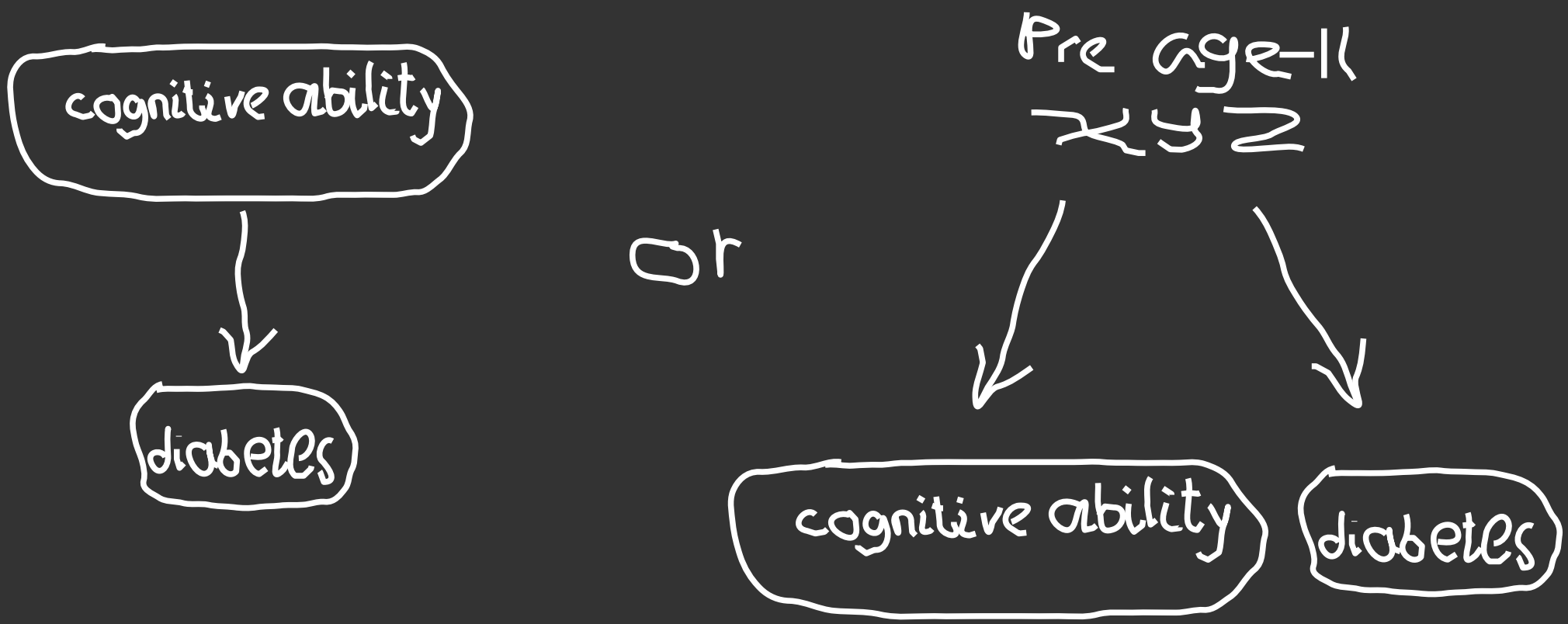

diabetes
cognitive ability

Lothian Birth Cohort 1936

- 1017people (513 men), all around 70 years old
- Cognitive ability measured at ages 11 and 70 years
- Diabetes measured at age 70 years:
  - 85 (8.4%) people with self-reported diabetes
  - HbA1C levels measured for all participants
  - HbA1C ≥ 6.5% = diabetes diagnosis (N = 116, 11.4%)


Cognitive ability
Cognitive ability
0.2
-0.2
-0.6
No diabetes
Some diabetes
Cognitive ability
0.2
-0.2
-0.6
Age 11
Age 70
Diabetes
No diabetes
age 70

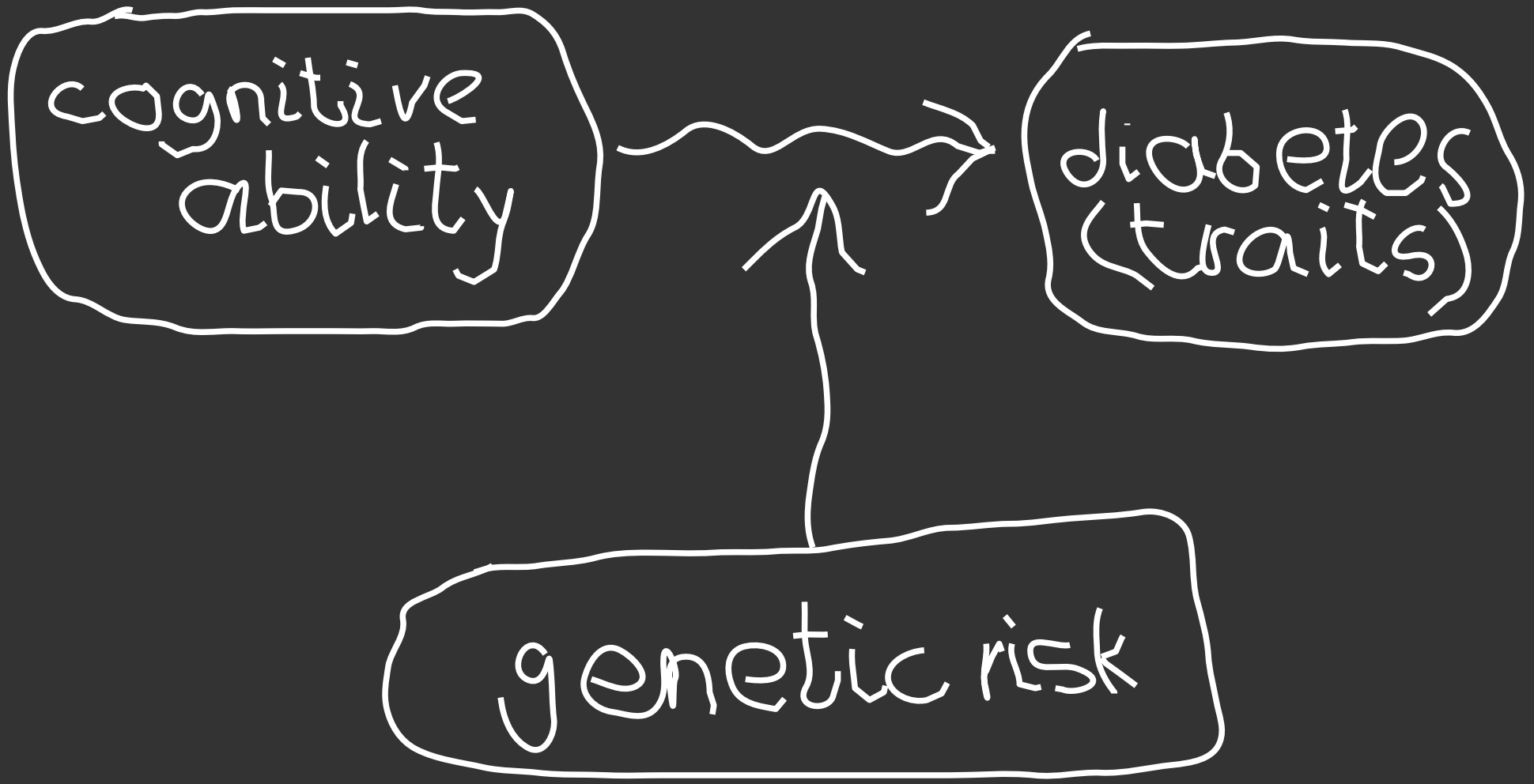

Cognitive ability
A.
Cognitive ability
0.2
-0.2
-0.6
B.
Cognitive ability
0.2
-0.2
-0.6
C.
Age 11
Age 70
Diabetes
No diabetes
age 70


cognitive ability
diabetes
or
Pre age-11
xyz
cognitive ability
diabetes

But what if bad is not always bad

- Low cognitive ability is bad for metabolism, possibly partly because it makes you do bad things to your body

- Maybe, if you have a 'good' body and you are therefore not constitutionally inclined towards bad metabolism, then however badly low cognition hits your body, your metabolism will resist
  - 'good body' ~ low genetic risk
  - diabetes and its quantitative markers (HbA1C) show reasonable heritability (> 60%)

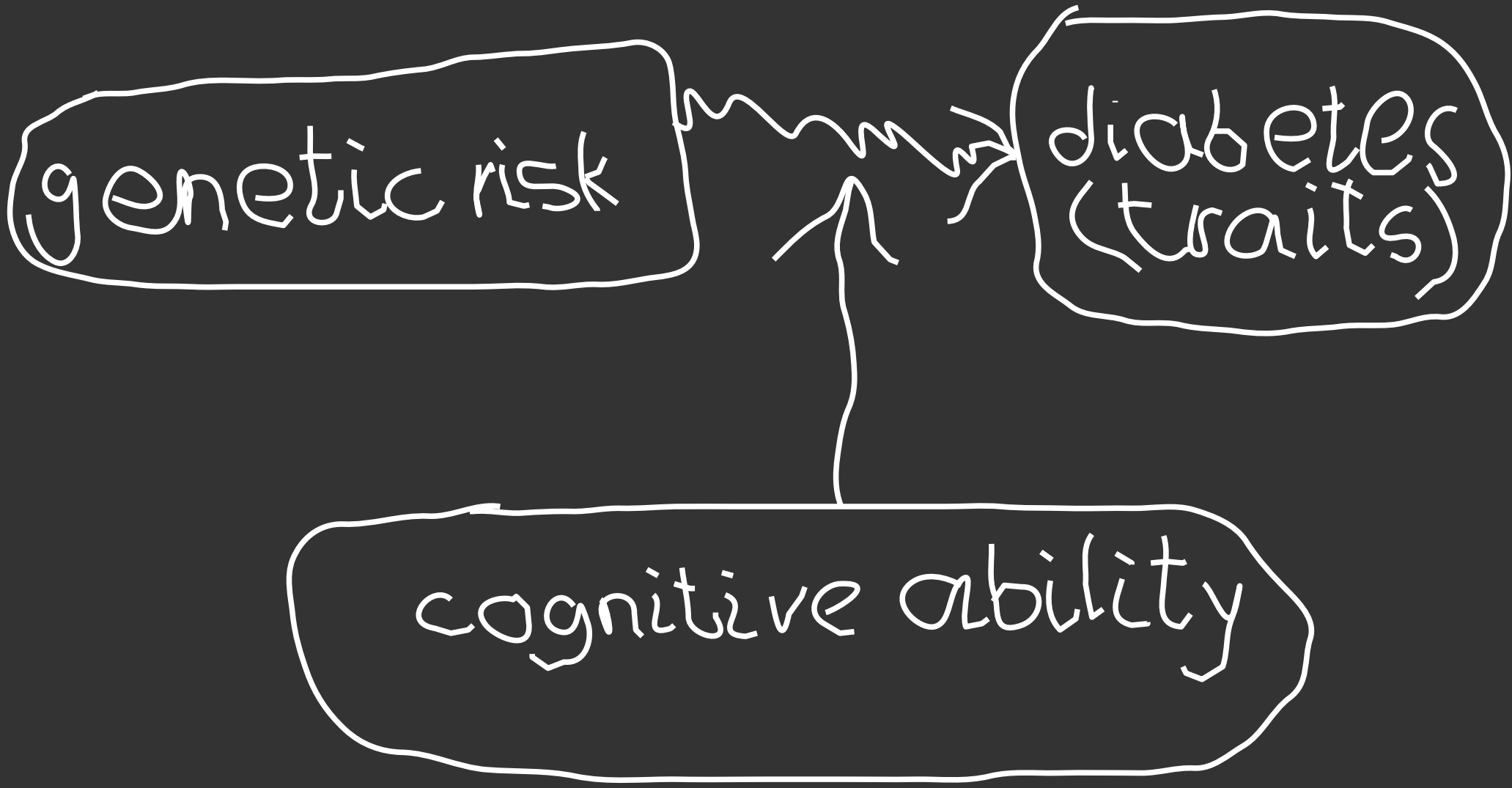

cognitive ability
diabetes (traits)
genetic risk

Can think about it the other way too

- It makes sense to hypothesize that manifestation of diabetes genetic risk may depend on cognitive ability:
  - low cognitive ability entails bad lifestyle choices, which facilitate genetic risk manifestation
  - high cognitive ability entails better lifestyle choices, which may buffer the effect of bad genes

Indeed

- Dietary habits may moderate type 2 diabetes risk manifestation (Qi et al., 2009; Cornelis et al., 2009; Nettleton et al., 2010)
- Physical activity may moderate obesity risk manifestation (Kilpeläinen et al., 2011)
- Both related to cognitive ability


genetic risk
diabetes (traits)
cognitive ability


cognitive ability
genetic risk
diabetes (traits)
(interaction)

Polygenic type 2 diabetes risk scores in 940 Lothian Birth Cohort 1936 members

- Large type 2 diabetes GWAS consortium (Voight et al.,2010)
  - 8,130 type 2 diabetes cases and 38,987 controls
  - Risk effect for the risk allele of each SNP
  - 8 sets of SNPs: p < 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0.01
- Used this to create 8 risk scores in our participants:
  - The number of risk alleles present * risk effect
  - The scores included ~ 196,000 to 2,600 alleles
- Number of alleles, age and sex co-varied in analyses

Main effects

- Polygenic risk scores had high intercorrelations:
  - r = 0.39 to 0.98 (median 0.81)
- Higher polygenic risk predicted diabetes:
  - OR 1.61 to 2.00 ($p < 0.001$) for diabetes diagnosis
  - r = 0.17 to 0.20 ($p < 0.001$) for HbA1C
- Higher age-11 predicted diabetes and higher HbA1C

Interactions

- Polygenic risk scores * cognitive ability:
  - p = 0.07 to 0.88 (median 0.13) for diabetes diagnosis (only 83 people with diabetes!)
  - p = 0.02 to 0.43 (median 0.03) for HbA1C

Cognitive ability had stronger effects among those at higher polygenic risk

- Childhood cognitive ability → HbA1C in below median polygenetic risk scores (N = 470):
  - -0.09 to -0.11 (p = 0.02 to 0.07)
- Childhood cognitive ability → HbA1C in above median polygenetic risk scores (N = 470):
  - -0.16 to -0.18 (p <= 0.001)

Risk scores had stronger effects among cognitively less able

- Polygenic risk scores → HbA1C in below median cognitive ability (N = 470):
  - r = 0.23 to 0.25 ($p < 0.001$)
- Polygenic risk scores → HbA1C in above median cognitive ability (N = 470):
  - r = 0.12 to 0.14 ($p < 0.01$)

Similar interaction trends for diabetes diagnosis

- Childhood cognitive ability → diabetes in below median polygenetic risk scores:
  - median OR = 0.81, range 0.68 to 0.88
- Childhood cognitive ability → diabetes in above median polygenetic risk scores:
  - median OR = 0.68, range 0.66 to 0 .761

Similar interaction trends for diabetes diagnosis

- Polygenic risk scores → diabetes in below median cognitive ability:
  - median OR = 2.23, range 1.90 to 2.45
- Polygenic risk scores → diabetes in above median cognitive ability:
  - median OR = 1.46, range 1.25 to 1.71

- Low cognitive ability may facilitate diabetes genetic risk manifestation, whereas high ability may buffer the risk by helping one to find a way around diabetes

- Or, put another way, 'good genes' may buffer against the effect of low cognitive ability and resulting unhealthy behaviours

- Results were not crystal clear!

- But they made sense

DIAbetes Genetics
Replication And Meta-analysis

Euroopa Liit
Euroopa Sotsiaalfond

Eesti tuleviku heaks